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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,244	01/28/2005	Peter Carmeliet	DECLE70.003APC	9196

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EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
11/19/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/502,244	CARMELIET ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 08/28/2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 06/04/2007 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 08/28/2007, claims 3-10 are pending in the application and response to applicant's arguments filed 08/28/2007 is moot in view of the new grounds of rejection below.

New Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof. The representative sample requirement may be satisfied by supplying structural or functional information, or a combination of both, such that one of skill in the art would be satisfied that applicants were in possession of the genus as claimed.

The instant claims are broadly drawn to a method of screening for molecules for the treatment of pathological angiogenesis comprising identifying molecules that inhibit the expression and/or activity of prominin-1 and monitoring the reduction in the number of blood vessels during the progression of a disease and further drawn to exposing prominin-1 or nucleic acids encoding prominin-1 to at least one molecule whose ability to reduce the number of blood vessels during the progression of the disease is sought to be determined, wherein determination is by binding of the prominin-1 to the molecule and wherein the binding is by immunoassay. The claims are further drawn to providing

a knock-out model that does not express prominin-1 and administering the molecule to be tested and measuring the formation of blood vessels during the progression of a disease.

At the outset it is noted that the rejected claims do not recite any sequence identifier relating to any prominin-1 gene or any pathological angiogenesis disease or disorder nor do the claims identify by name any particular angiogenic disorder or disease. At their most specific, the claims merely recite methods of identifying any molecule that inhibits the expression of prominin-1 or inhibits activity of prominin-1 or any transcript associated prominin-1 such that a reduction in the number of blood vessels is reduced in the progression of a disease thereby identifying a molecule for the treatment of pathological angiogenesis.

In contrast, the specification exemplifies, thru the use of a prominin-1 knock-out mouse model, mice deficient in prominin-1 showed reduced angiogenic response when subject to hyperpoxia and showed wound healing was impaired in prominin-1 deficient mice. The specification further exemplifies thru said knock-out mouse model, a decrease in the number of infiltrating leukocytes in tumors grown in prominin-1 deficient mice and a decrease in footpad thickness in a prominin-1 deficient mice injected with LPS to induce thrombosis. The examples in the specification are not considered to be representative of the breadth claimed, since the claims are very broadly drawn to methods of administering any compound that inhibits prominin-1 or inhibits expression of any gene or protein associated with the activity prominin-1 that results in the reduction of blood vessels during the progression of a disease.

The instant specification does not adequately describe what compounds could be administered that are commensurate in scope to what is now claimed. The claimed breadth reads on any molecule that can inhibit prominin-1 or inhibit any protein or gene involved in the activity prominin-1 such that a reduction of blood vessels occurs in the progression of a disease. Moreover, the instant specification does not provide any information on what compounds would inhibit the expression or activity of prominin-1 such that a treatment of any type of pathological angiogenesis occurs and one of skill in the art would not know what type of structure is capable of inhibiting promin-1 or the any activity associated with prominin-1. The instant specification is not considered to have described such breadth of molecules linked to such breadth of the claimed function of inhibiting prominin-1 and reducing of the number of blood cells. It is the lack of nexus linking such a broad genera of structures (any molecule targeted to any prominin-1 gene or any molecule targeted to any gene or protein associated with prominin-1 activity) with such a specific function (reducing blood vessel formation for the treatment of pathological angiogenesis) that necessitates this rejection.

The specification does not provide any specific guidance that would allow one the skilled artisan to recognize that Applicant was in possession of the instant invention, commensurate in scope with what is now claimed. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date sought, applicant was in possession of the claimed invention.

Claims 3-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The instant claims are drawn to a method of screening for molecules for the treatment of pathological angiogenesis comprising identifying molecules that inhibit the expression and/or activity of prominin-1 and monitoring the reduction in the number of blood vessels during the progression of a disease and further drawn to exposing prominin-1 or nucleic acids encoding prominin-1 to at least one molecule whose ability

to reduce the number of blood vessels during the progression of the disease is sought to be determined, wherein determination is by binding of the prominin-1 to the molecule and wherein the binding is by immunoassay. The claims are further drawn to providing a knock-out model that does not express prominin-1 and administering the molecule to be tested and measuring the formation of blood vessels during the progression of a disease.

The nature of the invention relies upon identifying molecules that inhibit prominin-1 or inhibit any activity associated with prominin-1 such that a reduction of blood vessels occurs during the progression of a disease which leads to a treatment of pathological angiogenesis.

Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b). The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date. 35 U.S.C. 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. > Chiron Corp. v.Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir.2004).

A thorough review of the patent and non-patent literature indicates that the state of the art linking prominin-1 and pathological angiogenesis was embryonic around the time of the instant invention. In 2000, Peichev et al. (of record) teach CD34+ cells, a distinct population of circulating cells, co-express AC133 (prominin-1) and VEGF and these distinct CD34+ cells have the capacity to migrate and differentiate into mature endothelial cells and play a major role in angiogenesis (see page 957, last paragraph). Similarly, Majka et al. (of record) in 2000 teach monitoring of the CD34+ cells, expressing AC133, for their ability to form haemotopoietic colonies after treatment with an antisense oligonucleotide targeted to AC133 (see page 58 and Figure 5). Neither Peichev et al. nor Majka et al. directly indicates inhibition of prominin-1 will lead to a reduction of the number of blood vessels during the progression of a disease and treatment of pathological angiogenesis thereof. Gehling et al. (Blood, May 2000) teach

AC133 derived cells have the ability to form new blood vessels when injected together with lung cancer cells but is silent as to the correlation between inhibition of AC133 or the activity of AC133 by any molecule and the reduction in blood vessels during the progression of a disease which would lead to a treatment of pathological angiogenesis in any disease or disorder.

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

While the level of one of ordinary skill practicing said invention would be high, the level of predictability is considered variable as evident in the prior art discussed above and is not considered to provide sufficient enablement to practice the claimed invention. At best, the prior art at the time of the instant invention invites further experimentation to find a correlation between inhibition of prominin-1 and a reduction in the number of

blood vessels during the progression of a disease such that treatment of a pathological disease occurs.

The working embodiment in the instant application illustrates mice deficient in prominin-1 showed reduced angiogenic response when subject to hyperpoxia and showed wound healing was impaired in prominin-1 deficient mice and further illustrates a decrease in the number of infiltrating leukocytes in tumors grown in prominin-1 deficient mice and a decrease in footpad thickness in a prominin-1 deficient mice injected with LPS to induce thrombosis. The working embodiment in the instant application does not include experiments linking inhibition of prominin-1 or the activity of prominin-1 by administration of a molecule with a reduction of blood vessels for the treatment of pathological disease in any disease or disorder. While the MPEP 2164.02 states the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970), the lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art.

Thus, as discussed above, there is no predictable correlation in the art for the role of prominin-1 in the treatment of pathological angiogenesis. Furthermore, given there is no guidance in the specification that would be considered enabling for the breadth of the claimed subject matter and the working embodiment of a prominin-1 knock-out murine model is not predictive of the inhibition of prominini-1 or any activity of prominin-1 by administration of a molecule such that a reduction of blood vessels

occurs and further the working embodiment is not predictive a treatment of pathological angiogenesis of any disease or disorder when prominin-1 is inhibited. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Response to Applicant's Arguments

Claim Rejections - 35 USC § 103

The rejection of claims 3-6 under 35 U.S.C. 103(a) as being unpatentable over Sirois, G. (US2003/0186920) in view of Peichev et al. (cited on PTO form 1449 filed 7/22/2004), Majka et al. (cited on PTO form 892 filed 12/19/2005) and Schmeisser et al. (Cardiovascular Research 2001, 49: 671-680) is withdrawn in view of the new grounds of rejections above.

The rejection of claims 3-10 under 35 U.S.C. 103(a) as being unpatentable over Sirois, G. (US2003/0186920), Peichev et al. (cited on PTO form 1449 filed 7/22/2004), Majka et al. (cited on PTO form 892 filed 12/19/2005) and Schmeisser et al. (Cardiovascular Research 2001, 49: 671-680) as applied to claims 3-6 above, and further in view of Babinet et al. (An. Acad. Bras. Cienc. 2001) and Murphy et al. (US 2003/0045489) is withdrawn in view of the new grounds of rejections above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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/Kimberly Chong/
Examiner AU 1635